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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,797	12/29/2000	Laure Dumoutier	LUD-5543.3 CONT.	5783

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FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,797	DUMOUTIER ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7,8,10,11,14-16,18,19 and 50-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *53-56* is/are allowed.

6)☒ Claim(s) *1, 3, 4, 7, 8, 10, 11, 14-16, 18, 19, 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 11/3/04, has been entered.

Applicant's amendment, filed on 11/3/04, has been entered.
Claims 53-56 have been added.

Claims 1, 3,4 7, 8, 10-11, 14-16, 18-19 and 56 are pending.

Claims 2, 5, 6, 9, 12-13, 17 and 20-49 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 11/3/04.
The rejections of record can be found in the previous Office Actions.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3, 4, 7, 8, 10, 14-16, 18-19 and 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while enabling for isolated nucleic acids which encode a T cell inducible factor which is a protein and which activates STAT3, which consists of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 (and vectors, recombinant cells comprising said nucleic acids)

does not reasonably providing enablement for the broader recitation of

nucleic acids which encode a T cell inducible factor which is a protein and which activates STAT3, the complementary sequence of which hybridizes under the claimed stringent conditions to at least one of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 (and vectors, recombinant cells comprising said nucleic acids) essentially for the reasons of record.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's assertions / arguments and the examiner's rebuttal are essentially the same of record.

Applicant asserts that the examiner has not rebutted the presumption that the specification enables the broad claim.

Applicant further asserts that there is no requirement exists in law that an applicant must disclose a structural basis or nexus of how a molecule functions and, in the instant case, there is absolutely no requirement that a claimed molecule which encodes and activates molecules, encode a direct ligand.

Applicant asserts that the hybridization conditions will perform the recited function.

In response to the use of non-prior art references in the rejection under 35 USC 112, first paragraph, enablement of record, applicant poses the following two questions.

(i) do these non-prior art references show that the molecules disclosed do not hybridize to SEQ ID NOS: 7, 8, 24 or 25, at the recited conditions of stringency?

(ii) do these non-prior art references show that the claimed molecules do not stimulate STAT3 production?

If applicant is asking whether the enablement references disclose that SEQ ID NOS 7, 8, 24 and/or 35 hybridize to these reference SEQ ID NOS. and stimulate STAT3; of course, the answer is no.

SEQ ID NOS 7, 8, 24 and 25 are the referenced sequences. The enablement rejection is not directed towards SEQ ID NOS. 7, 8, 24 and 25, but rather at the scope of asserted "isolated nucleic acids which encodes a T cell inducible factor which is a protein and activates STAT3" broadly encompassed by the claimed invention.

Applicant is reminded that the enablement rejection is one of scope, which indicates that SEQ ID NOS: 7, 8, 24 and 25 are enabled.

If applicant is asking whether the enablement references disclose or do not disclose molecules other than SEQ ID NOS: 7, 8, 24 and 25 have the same properties as these referenced sequence; the answer is no.

For that matter, neither has applicant. Applicant has not provided for those nucleic acids that encode "isolated nucleic acids which encodes a T cell inducible factor which is a protein and activates STAT3" other than the referenced SEQ ID NOS: 7, 8, 24 and 25.

With respect to Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000), applicant asserts that searching and identification of molecules via computerized homology searching is irrelevant to hybridization studies under clearly recited conditions.

While applicant relies upon hybridization studies rather than sequence homology per se, the hybridization studies are essentially relying upon sequence homology for hybridization to occur.

Furthermore, as pointed out previously, Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Therefore, the skilled artisan readily understood the lack of confidence and predictability between even among structurally related proteins based upon hybridization and/or sequence homology alone at the time the invention was made.

For example, applicant has not provided sufficient working examples as they read on the breadth of isolated nucleic acid molecules which encodes T cell inducible facrtors which is a protein and which activates STAT3, other than SEQ ID NOS: 7, 8, 24, and 25.

It has been noted that the claimed T cell inducible factor include T cell inducible factor (TIF) from other animal species, including other mammals as part of the invention (see page 29, lines 4-5 of the instant specification).

For example, claim 52 recites "murine T cell derived inducible factor", yet applicant has only disclosed a mouse T cell inducible factor and not a rat T cell inducible factor.

A number of molecules other than SEQ ID NO: 7, 8, 24 and 25 are able to stimulate STAT3 activation.

Again, the T cell inducible factors of the claimed invention do not activate STAT3 directly, but rather rely upon indirect and downstream signaling events. Whatever structure is being claimed is not the structure that actually activates STAT3 directly. Applicant has not disclosed nor identified the critical structural elements that would lead to an inducible T cell factor to stimulate STAT3. For example, it has been well known that the JAK kinases are responsible for STAT phosphorylation in response to cytokines.

Also, as pointed out previously, it was noted that the co-inventors have disclosed that the biological activities of T cell inducible factors remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse T cell inducible factor, T cell inducible factor does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, the reference distinguishes mouse from human T cell inducible factor as well as from in vitro and in vivo studies of T cell inducible factor (see Discussion). This discrepancy between in vitro and in vivo T cell inducible factor induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating T cell inducible factor (see Discussion).

Applicant appears to have ignored the complexities and discrepancies even among mouse and human T cell inducible factors, while at the same time asserting that the mouse and human T cell inducible factors set forth in SEQ ID NOS 7, 8, 24 and 25 provide sufficient enablement for a broad genus of nucleic acids encoding structural diverse T cell inducible factors from all mammalian species, which in turn, can stimulate downstream STAT3 activation events.

Applicant appears to be relying upon description of Examples of specific mouse and human TIF proteins and on the degeneracy of the genetic code without more precise guidelines amount to little more than a starting point, a direction for further research to enable the skilled artisan on how to make and use nucleic acids that encode TIFs from other animal species, including other mammals (e.g. see pages 28-30 of the instant specification). At most, the specification provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement for the scope of the claimed T cell inducible factors broadly encompassed by the claimed invention.

The following of record is reiterated for applicant's convenience.

The instant claims are drawn broadly to any nucleic acid that hybridizes to SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25 which encodes a T cell inducible factor (TIF) which is a protein and activates STAT3. However, the instant specification does not enable any such hybridizing nucleic acid broadly encompassed by the claimed invention.

It is noted that the claimed T cell inducible factor include T cell inducible factor (TIF) from other animal species, including other mammals as part of the invention (see page 29, lines 4-5 of the instant specification).

Further, it is noted that the claimed T cell inducible factors range from about 17-22 kD as determined by SDS-PAGE, which activate STAT proteins and in glycosylated form, these proteins range from 17 to about 30 kD, as determined by SDS-PAGE (see page 30, paragraph 2 of the instant specification).

Proteins encoded by the disclosed nucleic acids encompass immediate products of nucleic acid expression, glycosylated forms and multimeric forms comprising at least one protein of the invention or at least one different protein (see page 30, paragraph 1 of the instant specification).

Applicant has not disclosed an isolated nucleic acid molecule which encodes a T cell inducible factor (TIF) which activates STAT3, as recited in the instant claims, other than T cell inducible factors encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

Neither has applicant disclosed the structural basis or nexus for activation of STAT 3 by the T cell derived inducible factor (TIF) encoded by the disclosed nucleic acids consisting of cDNA and genomic sequences of TIF.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any mammalian T cell inducible factor. T cell inducible factor may have some notion of the function of the protein, however, there is insufficient guidance and direction as how to make and use the claimed genus of T cell inducible factors, commensurate in scope with the claimed invention. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

For example, the specification discloses a diversity of structure and function of the disclosed T cell inducible factors encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

It is noted that the instant specification discloses that mouse TIF beta and mouse TIF alpha respond differently in response to IL-9 (e.g. see Examples 12-14 on pages 15-17 of the instant specification).

Although the instant specification discloses high homology between mouse TIF alpha and beta (and therefore hybridizes to mouse TIF alpha under stringent conditions), there is insufficient guidance and direction as to critical common structural elements that define a T cell inducible factor or that define a T cell inducible factor alpha or beta and, in turn, the nexus between structure in an T cell inducible factor and its ability to stimulate the expression of STAT 3.

T cell inducible factors, including those encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25., which stimulate STAT 3, that is, they are not related as a ligand-receptor binding pair.

Consistent with the Examples in the instant specification (e.g. Examples 21 and 27), it is noted that the co-inventors have published the same or similar results disclosed in the specification as filed. For example, see Dumoutier et al. PNAS 97: 10144-10149, 2000 and Dumoutier et al., J. Immunol. 164: 1814-1819, 2000.

For example, the co-inventors have disclosed that the biological activities of T cell inducible factors remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse T cell inducible factor, T cell inducible factor does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, the reference distinguishes mouse from human T cell inducible factor as well as from in vitro and in vivo studies of T cell inducible factor (see Discussion). This discrepancy between in vitro and in vivo T cell inducible factor induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating T cell inducible factor (see Discussion).

This distinction between IL-9 and T cell inducible factors differs from the instant disclosure which states that T cell inducible factor is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

The co-inventors have disclosed that the mouse T cell inducible factors (TIF) were found to induce to STAT 3 and 5 activation in mesangial and neuronal cell lines but failed to reproduce activities such as the induction of proliferation of T helper clones, mast cells or inhibition of corticoid-induce apoptosis (Dumoutier et al., J. Immunol. 164: 1814-1819, 2000; see entire document, including Abstract and Discussion) (also see Example 21 of the instant specification).

In contrast to mouse IL-TIF, human IL-TIF induced STAT 1 and 3 in human hepatoma cells (see (Dumoutier et al. PNAS 97: 10144-10149, 2000) (See Example 27 of the instant specification).

It is noted that the starting material of peripheral blood cells for human TIF was stimulated with anti-CD3 antibodies and not IL-9 (see page 23, paragraph 1 of the instant specification). Anti-CD3 antibodies can stimulate a variety of molecules and are not limited to stimulating TIF alpha or beta. The instant specification further discloses that TIF mRNA can be expressed in the absence of IL-9 (see Example 14, particularly page 17, lines 7-8 of the instant specification.

In addition, it is noted that the "T cell inducible factor" has been renamed "IL-TIF/IL-21", which, in turn, has been renamed "IL-22" by the co-inventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1). Here, it is noted that the co-inventors have shown that the signaling pathways associated with IL-22 were not the same as IL-10, as previously thought (see entire document, including page 1, column 2, paragraph 2).

Furthermore, Ebert (Trends in Immunology 23: 341-342, 2002) notes confusion and ambiguities in labeling cytokines as interleukins, including IL-TIF/ IL-21 described by the instant inventor Dumoutier.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Applicant is relying upon certain biological activities and the disclosure of this limited number of mouse and human T cell inducible factor species to support an entire genus of nucleic acids encoding T cell inducible factors that stimulate STAT3 activation. Yet the instant specification does not provide sufficient guidance and direction how to make and use any nucleic acid that encodes a T cell inducible factor that stimulates STAT3 activation, as encompassed by the claims. Also, the specification does not provide for the correlation or nexus between the chemical structure and the function of the genus of T cell inducible factors or nucleic acids encoding T cell inducible factors, currently encompassed by the claimed invention. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. T cell inducible factor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a limited number of T cell inducible factor sequences from mouse and human and in turn utilizing predicted structural determinations to ascertain functional aspects of the genus of nucleic acids encoding T cell inducible factors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead the skilled artisan to make and use the genus of nucleic acids encoding T cell inducible factors (TIFs) which stimulate STAT3 in the claimed invention other than those disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a T cell inducible factor encoding a functional T cell inducible factor amino acid or nucleic acid structure as the relationship between structure-function was not well understood and was not predictable. Also, see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of nucleic acids encoding T cell inducible factors which stimulate STAT3 activation in the claimed invention.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use nucleic acids encoding T cell inducible factors which stimulate STAT 3 activation, under the high stringency conditions other than those disclosed as SEQ ID NOS 7, 8, 24 and 25 in the specification as filed

It is acknowledged that the instant specification does describe methods for screening and evaluating nucleic acid molecules that encode nucleic acid molecules which encode T cell inducible factors (TIFs) which also induce STAT3 activation.

However, the instant application does not provide the necessary link between these steps of screening and evaluating nucleic acids encoding T cell inducible factors. There is insufficient guidance in the way of selecting a T cell inducible factor without the need of undue experimentation. The instant application provides assays for determining whether a nucleic acid encodes a protein with certain desired characteristics (e.g. activates STAT3) and identifies certain specific T cell inducible factors from two mammalian species (mouse and human).

These descriptions without more precise guidelines amount to little more than a starting point, a direction for further research. The specification provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement for the scope of the claimed T cell inducible factors encompassed by the claimed invention.

Neither the specification nor the prior art provides a structural basis for the recited activity of the encoded protein. Without such guidance, predicting the structure that defines a TIF-IL/TIF-21 other than those IL-TIF/IL-21 encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25, and which possesses the claimed biological activities of stimulating STAT activation or acute phase production (other than an IL-TIFs/ IL-21 encoded by nucleic acid molecule consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25), is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986). In re Fisher, 166 USPQ 19, 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Therefore, there is insufficient evidence of record to show that one skilled in the art would be able to practice the scope of the claimed invention as claimed without an undue amount of experimentation.

Consequently, the experimentation left to those skilled in the art to determine which nucleic acid sequence variants of SEQ ID NOS: 7, 8, 24 and 25 would still maintain the properties of a T cell inducible factor (TIF) that activates STAT3 would have been unpredictable and, in turn, would have been unnecessarily, and improperly, extensive and undue. The instant application does not describe the claimed invention in terms that will enable the skilled artisan to make and use the invention, commensurate in scope with the claimed invention.

Applicant's arguments are not found persuasive.

5. Upon a review of the claimed nucleic acids, it is noted that dependent claim 3 recites "genomic DNA".

Given applicant's disclosure that the claimed T cell inducible factors includes T cell inducible factors (TIF) from other animal species, including other mammals as part of the invention (see page 29, lines 4-5 of the instant specification) and

that the claimed T cell inducible factors range from about 17-22 kD as determined by SDS-PAGE, which activate STAT proteins and in glycosylated form, these proteins range from 17 to about 30 kD, as determined by SDS-PAGE (see page 30, paragraph 2 of the instant specification),

the following rejection under 35 USC 112, first paragraph, written description has been set forth.

Claims 1, 3, 4, 7-8, 10-11, 14-16, 18-19, 50-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For example, the specification discloses a diversity of structure and function of the disclosed T cell inducible factors encoded by nucleic acid molecules consisting of SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25.

The specification discloses SEQ ID NOS: 7, 8 24 and 25 which corresponds to the cDNA encoding the human and mouse species of T cell derived inducible factors. SEQ ID NOS: 7, 8, 24 and 25 meet the written description provisions of 35 USC 112, first paragraph.

However, the instant claims to nucleic acids that encode T cell inducible factors, which encompass "genomic sequences" from "all mammalian species". The claimed nucleic acids encompass genomic sequences, sequences that hybridize to SEQ ID NOS: 7, 8, 24 and 25, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. Nucleic acid sequences other than SEQ ID NOS. 7, 8, 24 and 25 do not meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 7, 8, 24 and 25, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:
...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name nucleic acid molecule is not itself a written description of that DNA; it conveys insufficient distinguishing information concerning its identity. While the example provides a process for obtaining specific mouse and human T cell inducible factors (see Examples), there is insufficient further information in the application pertaining to that nucleic acids, including genomic nucleic acids as well as cDNA's, relevant structural or physical characteristics with respect to STAT 3 activation for example; in other words, it thus does not describe all nucleic acids, including genomic and cDNA encoding all or a sufficient number of T cell inducible factors from all mammals. Describing a method of preparing nucleic acid molecules such as cDNA or even describing the protein that the cDNA encodes, as the Examples do, does not necessarily describe the breadth of nucleic acid molecules encompassed by the claimed invention. There is insufficient sequence information indicating which nucleic acid molecules constitute genomic or cDNA for the number of mammalian species encompassed by the claimed nucleic acid molecules

For example, the specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art recognizes that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined. Therefore, the structure of these elements was not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid molecules, including genes and cDNAs from any mammalian species at the time the invention was made.

It is noted that the instant specification discloses that mouse TIF beta and mouse TIF alpha respond differently in response to IL-9 (e.g. see Examples 12-14 on pages 15-17 of the instant specification).

Although the instant specification discloses high homology between mouse TIF alpha and beta (and therefore hybridizes to mouse TIF alpha under stringent conditions), there is insufficient guidance and direction as to critical common structural elements that define a T cell inducible factor or that define a T cell inducible factor alpha or beta and, in turn, the nexus between structure in an T cell inducible factor and its ability to stimulate the expression of STAT3.

T cell inducible factors, including those encoded by SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 24 and SEQ ID NO: 25., which stimulate STAT 3, that is, they are not related as a ligand-receptor binding pair.

Consistent with the Examples in the instant specification (e.g. Examples 21 and 27), it is noted that the co-inventors have published the same or similar results disclosed in the specification as filed. For example, see Dumoutier et al. PNAS 97: 10144-10149, 2000 and Dumoutier et al., J. Immunol. 164: 1814-1819, 2000.

For example, the co-inventors have disclosed that the biological activities of T cell inducible factors remain illusive (Dumoutier et al. PNAS 97: 10144-10149, 2000; see entire document, particularly, page 10144, column 1, paragraph 1 of the Introduction). Further, this reference discloses that while IL-9 was useful in initially identifying mouse T cell inducible factor, T cell inducible factor does not appear to play a major role in the in vivo biological activities of IL-9 (see Discussion, page 10149, column 1, paragraph 1). Here, too, the reference distinguishes mouse from human T cell inducible factor as well as from in vitro and in vivo studies of T cell inducible factor (see Discussion). This discrepancy between in vitro and in vivo T

cell inducible factor induction might reflect an indirect mechanism of gene induction and that further studies are needed to elucidate the mechanisms of regulating T cell inducible factor (see Discussion).

This distinction between IL-9 and T cell inducible factors differs from the instant disclosure which states that T cell inducible factor is a marker for the expression or effect of IL-9 in a subject (see page 6 of the instant specification).

The co-inventors have disclosed that the mouse T cell inducible factors (TIF) were found to induce to STAT 3 and 5 activation in mesangial and neuronal cell lines but failed to reproduce activities such as the induction of proliferation of T helper clones, mast cells or inhibition of corticoid-induce apoptosis (Dumoutier et al., J. Immunol. 164: 1814-1819, 2000; see entire document, including Abstract and Discussion) (also see Example 21 of the instant specification).

In contrast to mouse IL-TIF, human IL-TIF induced STAT 1 and 3 in human hepatoma cells (see (Dumoutier et al. PNAS 97: 10144-10149, 2000) (See Example 27 of the instant specification).

It is noted that the starting material of peripheral blood cells for human TIF was stimulated with anti-CD3 antibodies and not IL-9 (see page 23, paragraph 1 of the instant specification). Anti-CD3 antibodies can stimulate a variety of molecules and are not limited to stimulating TIF alpha or beta. The instant specification further discloses that TIF mRNA can be expressed in the absence of IL-9 (see Example 14, particularly page 17, lines 7-8 of the instant specification.

In addition, it is noted that the "T cell inducible factor" has been renamed "IL-TIF/IL-21", which, in turn, has been renamed "IL-22" by the co-inventors (see page 1, column 1, Background and Prior Art of Renauld et al., US 2003/0012788 A1). Here, it is noted that the co-inventors have shown that the signaling pathways associated with IL-22 were not the same as IL-10, as previously thought (see entire document, including page 1, column 2, paragraph 2).

Furthermore, Ebert (Trends in Immunology 23: 341-342, 2002) notes confusion and ambiguities in labeling cytokines as interleukins, including IL-TIF/ IL-21 described by the instant inventor Dumoutier.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Applicant is relying upon certain biological activities and the disclosure of this limited number of mouse and human T cell inducible factor species to support an entire genus of nucleic acids encoding T cell inducible factors that stimulate STAT3 activation. Yet the instant specification does not provide sufficient guidance and direction how to make and use any nucleic acid that encodes a T cell inducible factor that stimulates STAT3 activation, as encompassed by the claims. Also, the specification does not provide for the correlation or nexus between the chemical structure and the function of the genus of T cell inducible factors or nucleic acids encoding T cell inducible factors, currently encompassed by the claimed invention. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and activities.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ▯ first paragraph, "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

While applicant relies upon hybridization conditions and a downstream STAT3 activation of cells The specification describes assays for determining whether a given nucleic acid molecule encodes a T cell inducible factor which is a protein which activates STAT3 that might work, this description without more precise guidelines amount to little more that a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute possession for the broad genus of nucleic acid molecules encoding T cell inducible factors from any mammalian species and encompassing genomic nucleic acids.

The instant disclosure does not provide for the possession of the functional characteristics of a genus of T cell inducible factor encoding nucleic acid molecules coupled with a known or disclosed correlation between the function of a T cell inducible factor with a particular structure and to stimulate a downstream or via indirect means STAT 3 activation encoded by nucleic acid molecules which hybridizes to SEQ ID NOS: 7,8, 24 and 25 under the written description provision of 35 USC 112, first paragraph.

Appellant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore, only SEQ ID NOS: 7, 8, 924 and 25 but not the full breadth of the claimed nucleic acid molecules meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant and there is insufficient disclosure and recitation of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

6. Claims 52-56 appear to be free of the prior art.
Accordingly, claims 52-56 are deemed allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300

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Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
February 7, 2005